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Provisional Application Cover Sheet

This is a Request for filing a PROVISIONAL APPLICATION under 37 C.F.R. 1.53(c)

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TITLE OF THE INVENTION (280 characters max)

IMIDAZOLINE DERIVATIVES HAVING CB_1-ANTAGONISTIC ACTIVITY

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of Pages 26	☐ Small Entity Statement
☐ Drawings	Number of Sheets	☐ Other Specify

METHOD OF PAYMENT (check one)

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Respectfully submitted,

SIGNATURE: Arthur S. Garrett	Date: February 19, 2004
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☐ Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FILING ONLY

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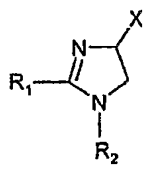
IMIDAZOLINE DERIVATIVES HAVING CB_1-ANTAGONISTIC ACTIVITY

The present invention relates to 1,2,4-tri-substituted imidazoline derivatives, to methods for the preparation of these compounds, to novel intermediates useful for the synthesis of said imidazoline derivatives, to methods for the preparation of these intermediates, to pharmaceutical compositions containing one or more of these imidazoline derivatives as active ingredient, as well as to the use of these pharmaceutical compositions for the treatment of psychiatric and neurological disorders.

Multisubstituted imidazoline derivatives are known from WO 03/101954 and WO 03/101969. The compounds described therein, are potent inhibitors of transcription factor NF-KB, making them useful in the treatment of certain types of tumors. Said imidazoline derivatives also have potent activities as anti-inflammatory agents and antibiotics, leading to an additional array of indications in which they are likely to be of therapeutic interest, including inflammatory and infectious diseases. The compounds described in the abovementioned patent applications were not demonstrated to have any affinity for cannabinoid receptors, and therefore unlikely to be of therapeutic value in disorders in which these cannabinoid receptors are involved.

The goal of the present invention was to identify imidazoline derivatives with potent activity as cannabinoid-CB_1 receptor modulators, whilst maintaining essentially the physico-chemical properties that make some imidazoline derivatives useful therapeutic agents.

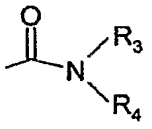
It has now surprisingly been found that potent antagonism or inverse agonism of cannabinoid-CB_1 receptors is present in the novel 4,5-dihydro-1H-imidazole derivatives of the formula (I):



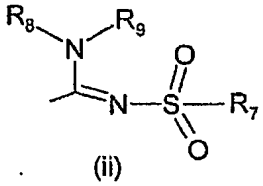
(I)

wherein

- R_1 and R_2 independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group branched or linear C_{1-3}-alkyl or C_{1-3}-alkoxy, phenyl, hydroxy, chloro, bromo, fluoro, iodo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R_1 and/or R_2 represent naphtyl,
- X represents one of the subgroups (i) or (ii),



(i)



(ii)

wherein

- R_3 represents a hydrogen atom or a branched or linear C_{1-3} alkyl group,
- R_4 represents a branched or linear C_{1-8} alkyl or C_{3-8}-cycloalkyl-C_{1-2}-alkyl group, branched or linear C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms, or R_4 represents a phenyl, phenoxy, benzyl, phenethyl or phenylpropyl group, optionally substituted on their phenyl ring with 1-3 substituents Y, wherein Y has the abovementioned meaning, or R_4 represents a pyridyl or thienyl group, or R_4 represents a group NR_5R_6 wherein

  R_5 and R_6 - together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl, phenyl, hydroxy or trifluoromethyl group or a fluoro atom, or

  R_3 and R_4 – together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) and which heterocyclic group may be

substituted with a branched or linear C_{1-3} alkyl, phenyl, amino, hydroxy or trifluoromethyl group or a fluoro atom,

- R_7 represents a benzyl, phenyl, thienyl or pyridyl group, which groups may be substituted on their aromatic ring with 1, 2, 3 or 4 substituents Y, wherein Y has the meaning as indicated above, which can be the same or different, or R_7 represents C_{1-8} branched or linear alkyl, C_{3-8} alkenyl, C_{3-10} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl or C_{5-8} cycloalkenyl or R_7 represents naphtyl or R_7 represents a amino group or R_7 represents a C_{1-8} dialkylamino group, a C_{1-8} monoalkylamino group or a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains 1 or 2 nitrogen atoms and which heterocyclic group may contain 1 heteroatom from the group (O, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl, phenyl, hydroxy or trifluoromethyl group or a fluoro atom,
- R_8 represent a hydrogen atom or a methyl group,
- R_9 represents a hydrogen atom or a methyl, ethyl or methoxy group

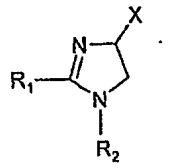
and tautomers, stereoisomers, prodrugs and salts thereof.

At least one centre of chirality is present (at the C_4 position of the imidazoline moiety) in the compounds of the formula (I). The invention relates to racemates, mixtures of diastereomers as well as the individual stereoisomers of the compounds having formula (I). The invention also relates to the E isomer, Z isomer and E/Z mixtures of compounds having formula (I).

Pro-drugs, i.e. compounds which when administered to humans by any known route, are metabolised to compounds having formula (I), belong to the invention. In particular this relates to compounds with primary or secondary amino or hydroxy groups. Such compounds can be reacted with organic acids to yield compounds having formula (I) wherein an additional group is present which is easily removed after administration, for instance, but not limited to amidine, enamine, a Mannich base, a hydroxyl-methylene derivative, an O-(acyloxymethylene carbamate) derivative, carbamate, ester, amide or enaminone. A pro-drug is an inactive compound, which when absorbed is

converted into an active form (Medicinal Chemistry: Principles and Practice, 1994, ISBN 0-85186-494-5, Ed.: F. D. King, p. 215).

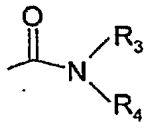
The invention particularly relates to compounds having formula (I)



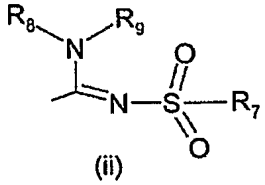
(I)

wherein

- R_1 and R_2 independently represent phenyl, which phenyl group may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group branched or linear C_{1-3}-alkyl or C_{1-3}-alkoxy, phenyl, hydroxy, chloro, bromo, fluoro, iodo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R_1 and/or R_2 represent naphtyl, thienyl or pyridyl,
- X represents one of the subgroups (i) or (ii),



(i)



(ii)

wherein

- R_3 represents a hydrogen atom,
- R_4 represents a branched or linear C_{1-8} alkyl, branched or linear C_{1-8} alkoxy or C_{3-8} cycloalkyl group, which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms, or R_4 represents a phenyl, phenoxy, pyridyl or thienyl group, or R_4 represents a group NR_5R_6 wherein

R_5 and R_6 - together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group

having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) or

R_3 and R_4 – together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a methyl, hydroxy or trifluoromethyl group or a fluoro atom,

- R_7 represents a phenyl group, which phenyl group may be substituted on its aromatic ring with 1, 2, 3 or 4 substituents Y, wherein Y has the meaning as indicated above, which can be the same or different, or R_7 represents C_{1-8} branched or linear alkyl, C_{3-10} cycloalkyl or C_{5-10} bicycloalkyl, or R_7 represents naphtyl or R_7 represents a amino group or R_7 represents a C_{1-8} dialkylamino group, a C_{1-8} monoalkylamino group or a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains 1 or 2 nitrogen atoms and which heterocyclic group may contain 1 heteroatom from the group (O, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl or hydroxy group,
- R_8 represents a hydrogen atom,
- R_9 represents a hydrogen atom

and tautomers, stereoisomers, prodrugs and salts thereof.

The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

Due to the potent CB_1 antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, in particular juvenile obesity and drug induced obesity, addiction, appetence, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease,

Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelinisation related disorders, as well as for the treatment of pain disorders, including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea, sexual disorders and cardiovascular disorders.

The cannabinoid receptor modulating activity of the compounds of the invention makes them particularly useful in the treatment of obesity, juvenile obesity and drug induced obesity, when used in combination with lipase inhibitors. Specific examples of compounds which can be used in such combination preparations are (but not restricted to) the synthetic lipase inhibitor orlistat, lipase inhibitors isolated from micro organisms such as lipstatin (from *Streptomyces toxytricini*), ebelactone B (from *Streptomyces aburaviensis*), synthetic derivatives of these compounds, as well as extracts of plants known to possess lipase inhibitory activity, for instance extracts of *Alpinia officinarum* or compounds isolated from such extracts like 3-methylethergalangin (from *A. officinarum*).

PHARMACOLOGICAL METHODS

In vitro affinity for cannabinoid-CB_1 receptors

The affinity of the compounds of the invention for cannabinoid CB_1 receptors can be determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabinoid CB_1 receptor is stably transfected in conjunction with [^{3}H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [^{3}H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand is performed by filtration over glassfiber filters. Radioactivity on the filter is measured by liquid scintillation counting.

***In vitro* cannabinoid-CB_1 receptor antagonism**

In vitro CB_1 receptor antagonism can be assessed with the human CB_1 receptor cloned in Chinese hamster ovary (CHO) cells. CHO cells are grown in a Dulbecco's Modified Eagle's medium (DMEM) culture medium, supplemented with 10% heat-inactivated fetal calf serum. Medium is aspirated and replaced by DMEM, without fetal calf serum, but containing [^{3}H]-arachidonic acid and incubated overnight in a cell culture stove (5% CO_2/95% air; 37 °C; water-saturated atmosphere). During this period [^{3}H]-arachidonic acid is incorporated in membrane phospholipids. On the test day, medium is aspirated and cells are washed three times using 0.5 mL DMEM, containing 0.2% bovine serum albumin (BSA). Stimulation of the CB_1 receptor by WIN 55,212-2 leads to activation of PLA_2 followed by release of [^{3}H]-arachidonic acid into the medium. This WIN 55,212-2-induced release is concentration-dependently antagonized by CB_1 receptor antagonists.

***In vivo* cannabinoid-CB_1 receptor antagonism**

In vivo CB_1 antagonism can be assessed with the CP-55,940-induced hypotension test in rat. Male normotensive rats (225-300 g; Harlan, Horst, The Netherlands) are anaesthetized with pentobarbital (80 mg/kg *i.p.*). Blood pressure is measured, via a cannula inserted into the left carotid artery, by means of a Spectramed DTX-plus pressure transducer (Spectramed B.V., Bilthoven, The Netherlands). After amplification by a Nihon Kohden Carrier Amplifier (Type AP-621G; Nihon Kohden B.V., Amsterdam, The Netherlands), the blood pressure signal is registered on a personal computer (Compaq Deskpro 386s), by means of a Po-Ne-Mah data-acquisition program (Po-Ne-Mah Inc., Storrs, USA). Heart rate is derived from the pulsatile pressure signal. All compounds are administered orally as a microsuspension in 1% methylcellulose 30 minutes before induction of the anesthesia which is 60 minutes prior to administration of the CB_1 receptor agonist CP-55,940. The injection volume is 10 ml/kg. After haemodynamic stabilization the CB_1 receptor agonist CP-55,940 (0.1 mg/kg *i.v.*) is administered and the hypotensive effect established. (Wagner, J. A.; Jarai, Z.; Batkai, S.; Kunos, G.

Hemodynamic effects of cannabinoids: coronary and cerebral vasodilation mediated by cannabinoid CB_1 receptors. *Eur.J.Pharmacol.* **2001**, *423*, 203-10).

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by mixing a compound of the present invention with a suitable acid, for instance an inorganic acid such as hydrochloric acid, or with an organic acid.

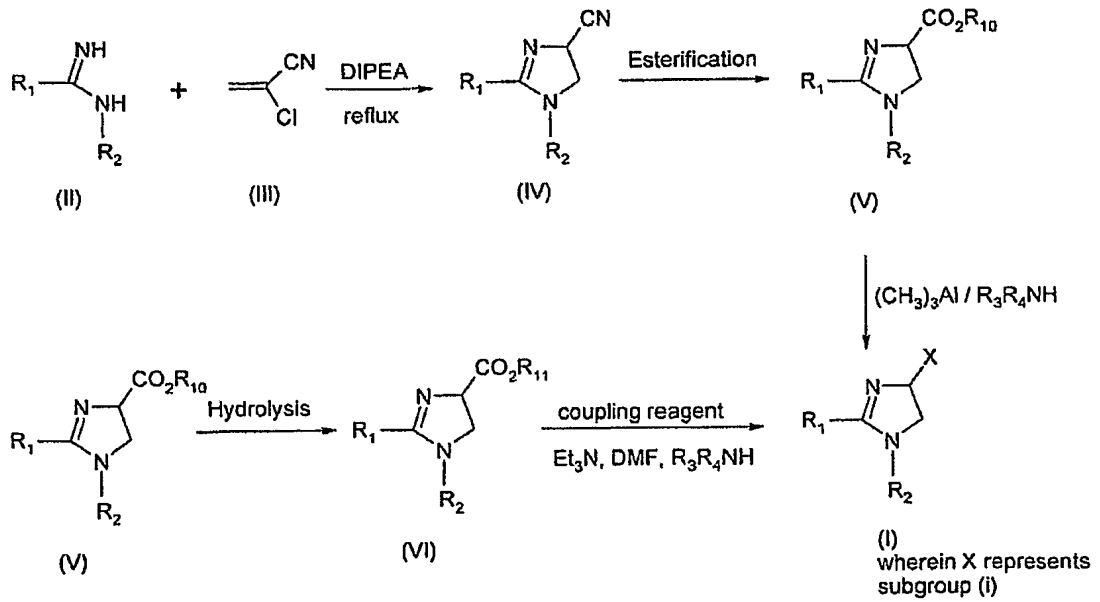
GENERAL ASPECTS OF SYNTHESES

The synthesis of compounds having formula (I) wherein X represents subgroup (i) is outlined in Scheme 1. Intermediates having general formula (II) can be obtained according to methods known, see for example: I. K. Khanna et al., J. Med. Chem. 2000, 43, 3168-3185, I. K. Khanna et al., J. Med. Chem. 1997, 40, 1634-1647 or WO 03/027076. Intermediates having general formula (IV) can be obtained according to methods known, see for example: I. K. Khanna et al., J. Med. Chem. 2000, 43, 3168-3185.
Carboxamidine derivatives of general formula (II) can be reacted with 2-chloroacrylonitrile (III) to give a 4,5-dihydro-1H-imidazole derivative of general formula (IV). This reaction is preferably carried out in the presence of a base such as N,N-diisopropylethylamine. The obtained derivatives of general formula (IV) can be esterified with an alcohol R_{10}-OH to give a 4,5-dihydro-1H-imidazole derivative of general formula (V), wherein R_{10} represents a branched or linear C_{1-5} alkyl group or a benzyl group. This reaction is preferably carried out under acidic conditions. A compound of general formula (V) can react with an amine R_3R_4NH, preferably in the presence of trimethylaluminum (Me_3Al) to give a compound of formula (I), wherein X represents subgroup (i) and R_3 and R_4 have the meaning as given above on page 2. Additional information on trimethylaluminum $Al(CH_3)_3$ promoted amidation reactions of esters can be found in: J. I. Levin, E. Turos, S. M. Weinreb, *Synth Commun.* (1982), *12*, 989-993.

Alternatively, a compound of general formula (V) can be hydrolysed to the corresponding carboxylic acid derivative of general formula (VI), wherein R_{11} represents H or an earth alkali metal, in particular Li, Na or K. The compound

of general formula (VI) can be reacted with a chlorinating agent such as thionylchloride to give the corresponding acid chloride. The compound of general formula (VI) can be reacted with an amine R_3R_4NH to give a compound of formula (I), wherein X represents subgroup (i) and R_3 and R_4 have the meaning as given above on page 2, *via* activating and coupling methods such as formation of an active ester, or in the presence of a so-called coupling reagent, such as for example, DCC, HBTU, BOP (benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate) and the like. Additional information on activating and coupling methods of amines to carboxylic acids can be found in:

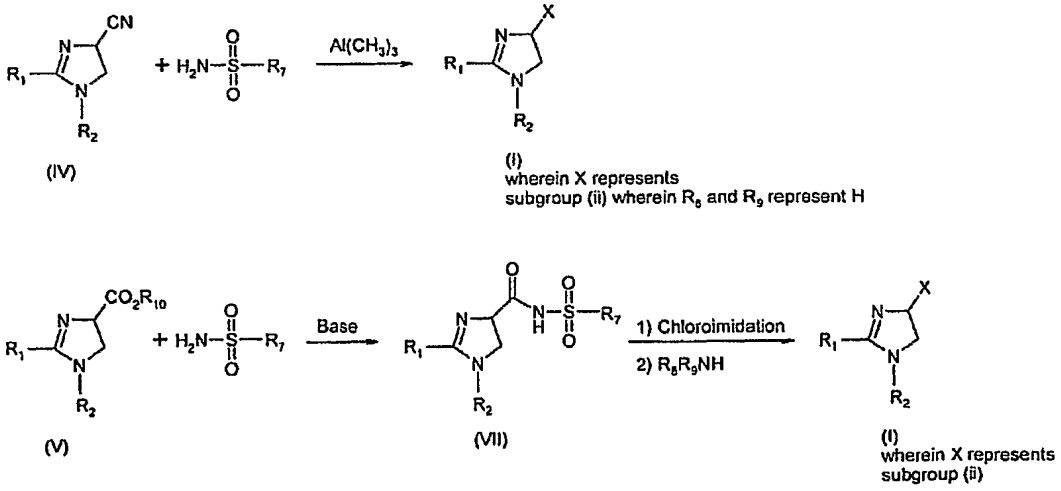
a) M. Bodanszky and A. Bodanszky: *The Practice of Peptide Synthesis*, Springer-Verlag, New York, **1994**; ISBN: 0-387-57505-7;
b) K. Akaji *et al.*, *Tetrahedron Lett.* (**1994**), 35, 3315-3318);
c) F. Albericio *et al.*, *Tetrahedron Lett.* (**1997**), 38, 4853-4856).



Scheme 1

The synthesis of compounds having formula (I) wherein X represents subgroup (ii) is outlined in Scheme 2.

An intermediate of general formula $R_7SO_2NH_2$ is either commercially available or can be prepared via standard synthetic methodology, for example from the corresponding compound R_7SO_2Cl (see for example; McManus et al., J. Med. Chem. 1965, 8, 766). A compound of general formula (IV) can be reacted with a compound of general formula $R_7SO_2NH_2$ in the presence of a Lewis acid such as for example $AlMe_3$ in an inert organic solvent such as benzene to give a compound of general formula (I) wherein X represents subgroup (ii) and R_1, R_2 and R_7 have the meaning as given above on the pages 1-3 and wherein R_8 and R_9 represent a hydrogen atom. A compound of general formula (V) may be reacted with a compound of general formula $R_7SO_2NH_2$ to give a compound of general formula (VII). This reaction is preferably carried out in the presence of a strong non-nucleophilic base. A compound of general formula (VII) may be reacted with a chlorinating reagent in a chloroimidation reaction and subsequently treated with an amine R_8R_9NH to give a compound of formula (I), wherein X represents subgroup (ii).



Scheme 2

The selection of the particular synthetic method depends on factors such as the compatibility of functional groups with the reagents used, the possibility to use protecting groups, catalysts, activating and coupling reagents and the ultimate structural features present in the final compound being prepared.

According to these procedures the following compounds can be prepared. They are intended to further illustrate the invention in more detail, and therefore are not deemed to restrict the scope of the invention in any way.

SYNTHESES OF SPECIFIC EXAMPLES

Examples 1 - 2

Part A: A magnetically stirred mixture of N-(4-chlorophenyl)-2,4-dichlorobenzenecarboxamidine (10.0 gram, 0.033 mol), 2-chloroacrylonitrile (5.7 gram, 0.065 mol) and N,N-diisopropylethylamine (DIPEA) (12.5 ml, 0.069 mol) in tetrahydrofuran (150 ml) is heated at reflux temperature for 40 hours (N_2 atmosphere). After cooling to room temperature the mixture is concentrated in vacuo. The residue is dissolved in a mixture of dichloromethane and water (200 ml/200 ml). The dichloromethane layer is collected, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is recrystallised from ethanol/water to give 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-dihydro-1H-imidazole-4-carbonitrile (11.23 gram, 97 % yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.28 (dd, J = 10 and 8 Hz, 1H), 4.36 (t, J = 10 Hz, 1H), 5.07 (dd, J = 10 and 8 Hz, 1H), 6.68 (br d, J = 8 Hz, 2H), 7.16 (br d, J = 8 Hz, 2H), 7.32-7.36 (m, 2H), 7.45 (d, J = 8 Hz, 1H).

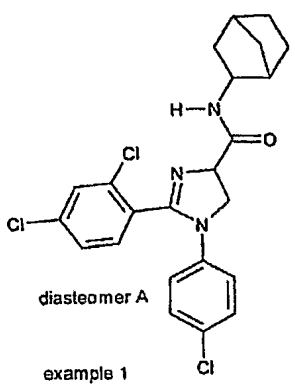
Part B: Acetyl chloride (17.76 ml, 0.25 mol) is slowly added to ethanol (1 l) to give solution A. 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-dihydro-1H-imidazole-4-carbonitrile (17.52 gram, 0.05 mol) is added in one portion to solution A. After cooling to room temperature the mixture is stirred for another 40 hours and concentrated in vacuo. The residue is dissolved in dichloromethane and washed (3x) with aqueous (5 %) $NaHCO_3$. The dichloromethane layer is separated, dried over $MgSO_4$, filtered and concentrated in vacuo to give ethyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-

4,5-dihydro-1H-imidazole-4-carboxylate (18.0 gram, 90 % yield) as a brown oil that slowly solidifies on standing. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.34 (t, J = 7 Hz, 3H), 4.15 (dd, J = 10 and 8 Hz, 1H), 4.22-4.41 (m, 3H), 4.91 (dd, J = 10 and 8 Hz, 1H), 6.66 (br d, J = 8 Hz, 2H), 7.11 (br d, J = 8 Hz, 2H), 7.30 (dd, J = 8 and 2 Hz, 1H), 7.33 (d, J = 2 Hz, 1H), 7.46 (dd, J = 8 Hz, 1H).

Part C: To a magnetically stirred solution of exo-2-aminobicyclo[2.2.1]heptane (0.67 ml, 0.009 mol) in anhydrous dichloromethane (10 ml) is added trimethylaluminum (5.4 ml of a 2N solution in hexane, 0.0108 mol) and the resulting solution is stirred for 20 minutes at room temperature. A solution of ethyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (2.385 g, 0.006 mol) in anhydrous dichloromethane (10 ml) is slowly added and the resulting mixture is reacted at 40 °C for 40 hours (N_2 atmosphere). After cooling to room temperature the mixture is quenched with aqueous (5 %) $NaHCO_3$ and extracted with dichloromethane. The dichloromethane layer is separated, dried over $MgSO_4$, filtered and concentrated in vacuo to give a crude yellow syrup (2.58 gram) which is further purified with flash chromatography (silica gel, ethyl acetate/petroleum ether = 8/2 (v/v)) to give the faster moving 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(exo-2-bicyclo[2.2.1]heptyl)-4,5-dihydro-1H-imidazole-4-carboxamide (diastereomer A) (0.70 gram, 25 % yield) and the slower moving 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(exo-2-bicyclo[2.2.1]heptyl)-4,5-dihydro-1H-imidazole-4-carboxamide (diastereomer B) (0.69 gram, 25 % yield).

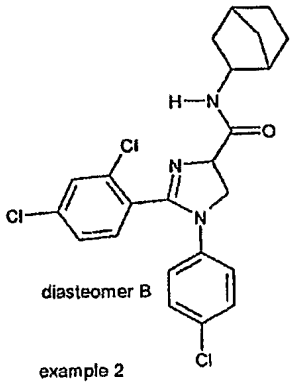
Diastereomer A: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.10-1.58 (m, 7H), 1.76-1.84 (m, 1H), 2.26-2.30 (m, 2H), 3.74-3.82 (m, 1H), 4.27 (d, J ~ 10 Hz, 2H), 4.78 (t, J ~ 10 Hz, 1H), 6.65 (br d, J = 8 Hz, 2H), 6.70-6.78 (m, 1H), 7.12 (br d, J = 8 Hz, 2H), 7.29 (br s, 2H), 7.40 (br s, 1H).

Diastereomer B: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.10-1.56 (m, 7H), 1.78-1.85 (m, 1H), 2.17-2.20 (m, 1H), 2.26-2.30 (m, 1H), 3.76-3.82 (m, 1H), 4.25-4.30 (m, 2H), 4.78 (dd, J = 10 and 8 Hz, 1H), 6.66 (br d, J = 8 Hz, 2H), 6.80 (br d, J ~ 7 Hz, 1H), 7.11 (br d, J = 8 Hz, 2H), 7.30 (br s, 2H), 7.41 (br s, 1H).



diasteomer A

example 1



diasteomer B

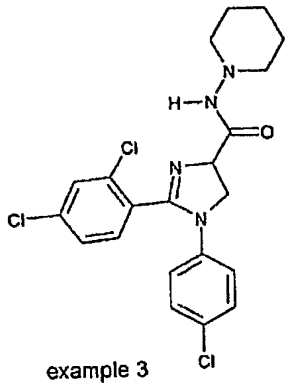
example 2

Examples 3 and 4

Part A: A mixture of ethyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (3.97 g, 0.01 mol) in methanol/water is reacted with LiOH (1.3 gram, 0.054 mol) at room temperature for 16 hours. The resulting mixture is concentrated in vacuo to give crude lithium 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (4.7 gram).

Part B: A mixture of the crude lithium 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (1.0 gram, ~ 0.0027 mol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) (1.2 gram, 0.0027 mol), 1-aminopiperidine (0.3 gram, 0.003 mol) and triethylamine (1 ml) in DMF (30 ml) is stirred at room temperature for 16 hours. After concentration in vacuo, water is added and the resulting mixture is extracted (2x) with dichloromethane. The dichloromethane layers are collected, dried over $MgSO_4$, filtered and concentrated in vacuo to give a residue that is further purified by flash chromatography (silicagel, dichloromethane/methanol = 95/5 (v/v)) to give 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-4,5-dihydro-1H-imidazole-4-carboxamide (380 mg, 31 % yield). Melting point: 113-116 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.33-1.48 (m, 2H), 1.60-1.80 (m, 4H), 2.68-2.82 (m, 4H), 4.28-4.35 (m, 2H), 4.84 (dd, J = 11 and 9 Hz, 1H),

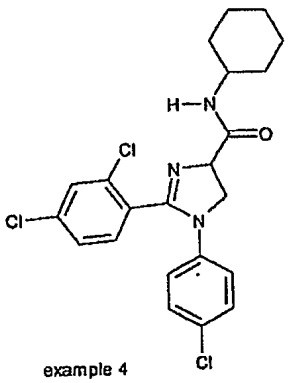
6.65 (br d, J = 8 Hz, 2H), 7.11 (br d, J = 8 Hz, 2H), 7.23-7.33 (m, 2H), 7.41 (d, J = 2 Hz, 1H), 7.57 (br s, 1H).



example 3

In an analogous manner example 4 was prepared:

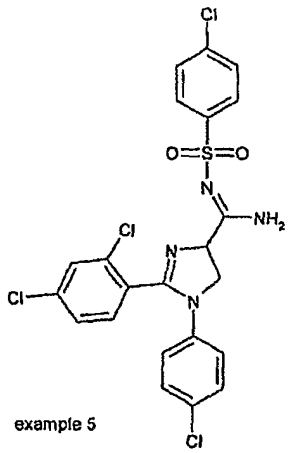
Example 4: 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N-cyclohexyl-4,5-dihydro-1H-imidazole-4-carboxamide. Melting point: 127-129 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.04-2.03 (m, 10H), 3.73-3.92 (m, 1H), 4.23-4.33 (m, 2H), 4.81 (t, J ~ 10 Hz, 1H), 6.66 (br d, J = 8 Hz, 2H), 6.79 (br d, J ~ 7 Hz, 1H), 7.12 (br d, J = 8 Hz, 2H), 7.25-7.32 (m, 2H), 7.41 (br s, 1H).



example 4

Examples 5 – 8

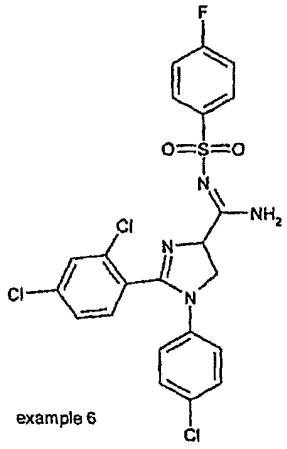
Part A: To a suspension of 4-chlorobenzenesulfonamide (0.45 gram, 0.00236 mol) in benzene (5 ml) is dropwise added trimethylaluminum (1.2 ml of a 2N solution in toluene, 0.0024 mol) to give a clear solution which is stirred at room temperature for 1 hour. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-4,5-dihydro-1H-imidazole-4-carbonitrile (0.55 gram, 0.00157 mol) is added and the resulting mixture is heated at 90 °C for 16 hours. After cooling to room temperature a mixture of methanol/water (8/2 (v/v)) is slowly added, the solids are removed by filtration and washed with chloroform (50 ml). The filtrate is concentrated in vacuo. The residue is triturated with n-pentane and twice recrystallised from methanol to give 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-1H-imidazole-4-carboxamidine (0.435 gram, 51 % yield). Melting point: 165-166 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.11-4.35 (m, 2H), 4.94 (dd, J =12 and 10 Hz, 1H), 6.63 (br d, J = 8 Hz, 2H), 7.12 (br d, J = 8 Hz, 2H), 7.22-7.52 (m, 6H), 7.90 (br d, J = 8 Hz, 2H), 8.10-8.20 (m, 1H).



example 5

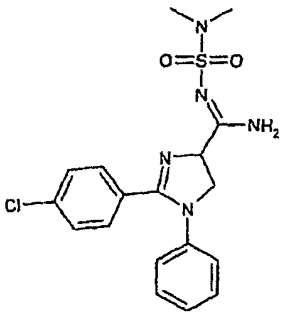
In an analogous manner the compounds having formula (I) listed below have been prepared:

Example 6: 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(4-fluorophenyl)-sulfonyl]-4,5-dihydro-1H-imidazole-4-carboxamidine. Melting point: 172-175 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.12-4.35 (m, 2H), 4.93 (dd, J =12 and 10 Hz, 1H), 6.63 (br d, J = 8 Hz, 2H), 7.08-7.43 (m, 8H), 7.90-8.02 (m, 2H), 8.10-8.20 (m, 1H).



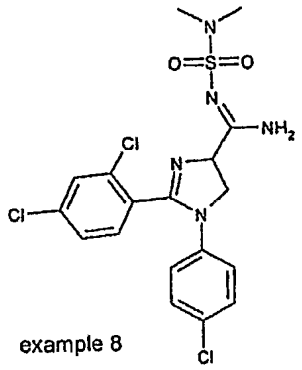
example 6

Example 7: 2-(4-Chlorophenyl)-N-(dimethylaminosulfonyl)-1-phenyl-4,5-dihydro-1H-imidazole-4-carboxamidine. Melting point: 136-139 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.79 (s, 6H), 4.20-4.40 (m, 2H), 4.97 (t, J ~ 10 Hz, 1H), 6.83 (br d, J = 8 Hz, 2H), 7.05-7.50 (m, 8H), 7.80-7.90 (m, 1H).



example 7

Example 8: 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(dimethylaminosulfonyl)-4,5-dihydro-1H-imidazole-4-carboxamidine. Melting point: 146-147 °C.



example 8

FORMULATIONS OF COMPOUNDS AS USED IN ANIMAL STUDIES

Formulation of example 1:

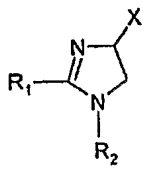
For oral *(p.o.)* administration: to the desired quantity (0.5-15 mg) of the compound given above as 'Example 1' in a glass tube, some glass beads were added and the substance was milled by vortexing for 2 minutes. After addition of 1 ml of a solution of 1% methylcellulose in water, the compound was suspended by vortexing for 10 minutes. For concentrations up and above 1 mg/ml remaining particles in the suspension were further suspended by using an ultrasonic bath.

PHARMACOLOGICAL TESTRESULTS

Example number	Human cannabinoid-CB_1 receptor *In vitro* affinity: pK_i value
Example 1	7.3
Example 2	7.0
Example 4	7.1
Example 8	7.4

CLAIMS

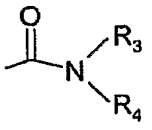
1. Compounds of the general formula (I)



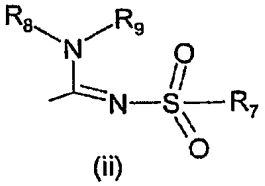
(I)

wherein

- R_1 and R_2 independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group branched or linear C_{1-3}-alkyl or C_{1-3}-alkoxy, phenyl, hydroxy, chloro, bromo, fluoro, iodo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R_1 and/or R_2 represent naphtyl,
- X represents one of the subgroups (i) or (ii),



(i)



(ii)

wherein

- R_3 represents a hydrogen atom or a branched or linear C_{1-3} alkyl group,
- R_4 represents a branched or linear C_{1-8} alkyl or C_{3-8}-cycloalkyl-C_{1-2}-alkyl group, branched or linear C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms, or R_4 represents a phenoxy, benzyl, phenethyl or phenylpropyl group, optionally substituted on their phenyl ring with 1-3 substituents Y, wherein Y has the abovementioned meaning, or R_4 represents a pyridyl or thienyl group, or R_4 represents a group NR_5R_6 wherein

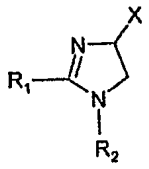
R_5 and R_6 - together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl, phenyl, hydroxy or trifluoromethyl group or a fluoro atom, or

R_3 and R_4 – together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl, phenyl, amino, hydroxy or trifluoromethyl group or a fluoro atom,

- R_7 represents a benzyl, phenyl, thienyl or pyridyl group, which groups may be substituted on their aromatic ring with 1, 2, 3 or 4 substituents Y, wherein Y has the meaning as indicated above, which can be the same or different, or R_7 represents C_{1-8} branched or linear alkyl, C_{3-8} alkenyl, C_{3-10} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl or C_{5-8} cycloalkenyl or R_7 represents naphtyl or R_7 represents a amino group or R_7 represents a C_{1-8} dialkylamino group, a C_{1-8} monoalkylamino group or a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains 1 or 2 nitrogen atoms and which heterocyclic group may contain 1 heteroatom from the group (O, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl, phenyl, hydroxy or trifluoromethyl group or a fluoro atom,
- R_8 represent a hydrogen atom or a methyl group,
- R_9 represents a hydrogen atom or a methyl, ethyl or methoxy group,

and tautomers, stereoisomers, prodrugs and salts thereof

2. Compounds of the general formula (I)

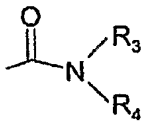


(I)

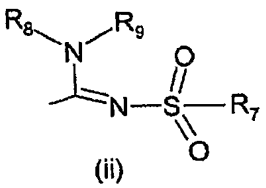
wherein

- R_1 and R_2 independently represent phenyl, which phenyl group may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group branched or linear C_{1-3}-alkyl or C_{1-3}-alkoxy, phenyl, hydroxy, chloro, bromo, fluoro, iodo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R_1 and/or R_2 represent naphtyl, thienyl or pyridyl,

- X represents one of the subgroups (i) or (ii),



(i)



(ii)

wherein

- R_3 represents a hydrogen atom,
- R_4 represents a branched or linear C_{1-8} alkyl, branched or linear C_{1-8} alkoxy or C_{3-8} cycloalkyl group, which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms, or R_4 represents a phenoxy, pyridyl or thienyl group, or R_4 represents a group NR_5R_6 wherein

R_5 and R_6 - together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) or

R_3 and R_4 – together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or two heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a methyl, hydroxy or trifluoromethyl group or a fluoro atom,

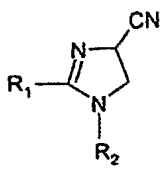
- R_7 represents a phenyl group, which phenyl group may be substituted on its aromatic ring with 1, 2, 3 or 4 substituents Y, wherein Y has the meaning as indicated above, which can be the same or different, or R_7 represents C_{1-8} branched or linear alkyl, C_{3-10} cycloalkyl or C_{5-10} bicycloalkyl, or R_7 represents naphtyl or R_7 represents a amino group or R_7 represents a C_{1-8} dialkylamino group, a C_{1-8} monoalkylamino group or a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains 1 or 2 nitrogen atoms and which heterocyclic group may contain 1 heteroatom from the group (O, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl or hydroxy group,
- R_8 represent a hydrogen atom,
- R_9 represents a hydrogen atom

and tautomers, stereoisomers, prodrugs and salts thereof.

3. Pharmaceutical compositions containing a pharmacologically active amount of at least one compound as claimed in claim 1 or claim 2, or a salt thereof, as an active component.

4. A compound as claimed in claim 1 or claim 2, or a salt thereof, for use in medicine

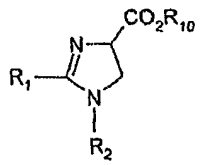
5. Compounds of the general formula (IV)



(IV)

wherein R_1 and R_2 have the meanings given in claim 1, such compounds being useful in the synthesis of compounds of the general formula (I).

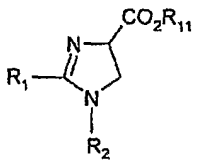
6. Compounds of the general formula (V)



(V)

wherein R_1 and R_2 have the meanings given in claim 1 and R_{10} represents a branched or linear C_{1-5} alkyl group or a benzyl group, such compounds being useful in the synthesis of compounds of the general formula (I).

7. Compounds of the general formula (VI)



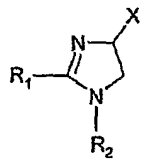
(VI)

wherein R_1 and R_2 have the meanings given in claim 1 and R_{11} represents H or an earth alkali metal, such compounds being useful in the synthesis of compounds of the general formula (I).

8. Use of a compound as claimed in claim 1 or claim 2 for the preparation of a pharmaceutical composition for the treatment of psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, in particular juvenile obesity and drug induced obesity, addiction, appetence, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke,

Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelinisation related disorders, as well as for the treatment of pain disorders, including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea, sexual disorders and cardiovascular disorders.

9. A method of treating psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, drug dependence and neurological disorders such as dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma as well as for the treatment of neuropathic pain disorders and other diseases involving cannabinoid neurotransmission, including glaucoma, cancer, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea, sexual disorders and cardiovascular disorders,
characterized in that a compound of formula (I) is used



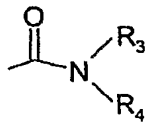
(I)

wherein

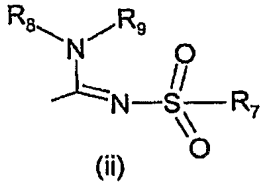
- R_1 and R_2 independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group C_{1-3}-alkyl or C_{1-3}-alkoxy, phenyl, hydroxy, chloro, bromo, fluoro, iodo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy,

methylsulfonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R_1 and/or R_2 represent naphtyl,

- X represents one of the subgroups (i) or (ii),



(i)



(ii)

wherein

- R_3 represents a hydrogen atom or a branched or linear C_{1-3} alkyl group,
- R_4 represents a branched or linear C_{1-8} alkyl or C_{3-8}-cycloalkyl-C_{1-2}-alkyl group, branched or linear C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl, which groups may contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with a hydroxy group, 1-3 methyl groups, an ethyl group or 1-3 fluoro atoms, or R_4 represents a phenyl, phenoxy, benzyl, phenethyl or phenylpropyl group, optionally substituted on their phenyl ring with 1-3 substituents Y, wherein Y has the abovementioned meaning, or R_4 represents a pyridyl or thienyl group, or R_4 represents a group NR_5R_6 wherein

  R_5 and R_6 - together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl, phenyl, hydroxy or trifluoromethyl group or a fluoro atom, or

  R_3 and R_4 – together with the nitrogen atom to which they are attached - form a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains one or more heteroatoms from the group (O, N, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl, phenyl, amino, hydroxy or trifluoromethyl group or a fluoro atom,
- R_7 represents a benzyl, phenyl, thienyl or pyridyl group, which groups may be substituted on their aromatic ring with 1, 2, 3 or 4 substituents Y,

wherein Y has the meaning as indicated above, which can be the same or different, or R_7 represents C_{1-8} branched or linear alkyl, C_{3-8} alkenyl, C_{3-10} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl or C_{5-8} cycloalkenyl or R_7 represents naphtyl or R_7 represents a amino group or R_7 represents a C_{1-8} dialkylamino group, a C_{1-8} monoalkylamino group or a saturated or unsaturated, monocyclic or bicyclic, heterocyclic group having 4 to 10 ring atoms, which heterocyclic group contains 1 or 2 nitrogen atoms and which heterocyclic group may contain 1 heteroatom from the group (O, S) and which heterocyclic group may be substituted with a branched or linear C_{1-3} alkyl, phenyl, hydroxy or trifluoromethyl group or a fluoro atom,

- R_8 represent a hydrogen atom or a methyl group,
- R_9 represents a hydrogen atom or a methyl, ethyl or methoxy group,

and tautomers, stereoisomers, prodrugs and salts thereof.

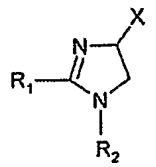
10. Use as claimed in claim 8 characterized in that said disorders are eating disorders, in particular obesity, juvenile obesity and drug induced obesity.

11. Use of a compound as claimed in claim 1 or claim 2 for the preparation of a pharmaceutical composition for the treatment of eating disorders, in particular obesity, juvenile obesity and drug induced obesity, characterized in that said pharmaceutical composition also contains at least one lipase inhibitor.

12. Use as claimed in claim 11, characterized in that said lipase inhibitor is orlistat or lipstatin.

Abstract

The present invention relates to 1,2,4-tri-substituted imidazoline derivatives, to methods for the preparation of these compounds, to novel intermediates useful for the synthesis of said imidazoline derivatives, to methods for the preparation of these intermediates, to pharmaceutical compositions containing one or more of these imidazoline derivatives as active ingredient, as well as to the use of these pharmaceutical compositions for the treatment of psychiatric and neurological disorders. The compounds have the general formula (I)



(I)

wherein the symbols have the meanings given in the specification.